AMENDMENTS TO THE SPECIFICATION

Please amend the specification, as follows:

Please replace the paragraph appearing at page 7, line 20 to page 8, line 7 with the following amended paragraph:

According to further preferred embodiments of the aforementioned method of the present invention, there are provided the above method wherein the polymer carrier is those having carboxyl groups, preferably a polysaccharide derivative having carboxyl groups; the above method wherein the polymer carrier is a carboxy(C_{1-4})alkyldextran polyalcohol, preferably carboxymethyldextran polyalcohol; the above method wherein the dextran polyalcohol that constitutes the carboxy(C_{1-4})alkyldextran polyalcohol is a dextran polyalcohol which is obtained by treating a dextran under conditions that enable substantially complete polyalcoholization; the above method wherein the polymer carrier is modified with a saccharide compound; the above method wherein the drug compound introduced to the DDS compound is an antineoplastic agent or an anti-inflammatory agent; the above method wherein the spacer is a tetrapeptide represented as, from the N-terminal, -Gly-Gly-Phe-Gly- (SEQ ID NO. 1) or a tetrapeptide represented as, from the N-terminal, -Gly-Gly-Gly-Phe- (SEQ ID NO. 8); the above method wherein the spacer is a group represented as, from the N-terminal, -Gly-Gly-Phe-Gly-NH-Y'-CH_2-O-CO- (SEQ ID NO. 1) or -Gly-Gly-Gly-Phe-NH-Y'-CH_2-O-CO- (SEQ ID NO. 8) wherein Y' represents p-phenylene group; the above method wherein the peptidase is α-chymotrypsin or papain; and the above method wherein the drug compound is (1S,9S)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13(9H,15H)-dione.

Please replace the paragraph appearing at page 8, lines 8 to 19 with the following amended paragraph:

According to a particularly preferred embodiment of the above method of the present invention, the above method can be used for measurement of a DDS compound in which a carboxy(C_{1-4})alkyldextran polyalcohol and (1S,9S)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13(9H,15H)-dione are bound to each other by means of a spacer comprising a tetrapeptide represented as, from the N-terminal, -Gly-Gly-Phe-Gly- (SEQ ID NO. 1) or a tetrapeptide represented as, from the N-terminal, -Gly-Gly-Gly-Phe- (SEQ ID NO. 8), and the DDS compound or a content of the antineoplastic agent introduced to the DDS compound can be measured by using α-chymotrypsin as the peptidase, and by measuring (1S,9S)-9-ethyl-5-fluoro-1-glycylamino-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo-[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13(9H,15H)-dione as the hydrolysate.

Please replace the paragraph appearing at page 13, line 26 to page 14, line 7 with the following amended paragraph:

Specific examples of oligopeptides that can be used as the spacer are shown in the following table; however, spacers used for the DDS compounds of the present invention are not limited to those mentioned below. It can be readily understood that one of ordinary skilled in the art can appropriately determine whether or not a spacer is used, or choose the type of a spacer when a spacer is used so as to achieve an optimum releasing rate of a drug compound. In the table, the left ends of peptide sequences are N-terminals and the residues of drug compounds are bound to C-terminals. D-Phe represents the D-phenylalanine residue and the other amino acids represent L-amino acids. The degrees of the releasing rate were judged from the degree of appearance of efficacy of the DDS compounds carrying doxorubicin against Walker 256 tumor-bearing rats, or from free doxorubicin concentrations at tumorous sites of Walker 256 tumor-bearing rats. For doxorubicin, a spacer that can release the drug compound at a high concentration immediately, e.g., -Gly-Gly-Phe-Gly- (SEQ ID NO. 1), is preferably used among the listed spacers.

Please replace Table 1, at page 14-15, with the following amended Table 1:

Table 1

(a) Spacers having high releasing rate

-Leu-Gly-

-Tyr-Gly-

-Phe-Gly-

-Gly-Phe-Gly-

-Gly-Gly-Phe-Gly- (SEQ ID NO. 1)

-Gly-Phe-Gly-Gly- (SEQ ID NO. 2)

-Phe-Gly-Gly-Gly- (SEQ ID NO. 3)

-Phe-Phe-Gly-Gly- (SEQ ID NO. 4)

-Gly-Gly-Gly-Phe-Gly- (SEQ ID NO. 5)

(b) Spacers having relatively high releasing rate

-Gly-Gly-Phe-Phe- (SEQ ID NO. 6)

-Gly-Gly-Gly-Gly-Gly-Gly- (SEQ ID NO. 7)

(c) Spacers having relatively low releasing rate

-Phe-Phe-

-Ala-Gly-

-Pro-Gly-

-Gly-Gly-Gly-Phe- (SEQ ID NO. 8)

(d) Spacers having low releasing rate

-Gly-

-D-Phe-Gly-

-Gly-Phe-

-Ser-Gly-

-Gly-Gly-

-Gly-Gly-Gly-

-Gly-Gly-Gly-Gly- (SEQ ID NO. 9)

Please replace the paragraph appearing at page 21, line 30 to page 22 with the following amended paragraph:

The DDS compound of the present invention is characterized in that it can specifically exhibit desired pharmacological activity at a local site such as tumorous sites or inflammatory sites depending on the sort of a residue of a drug compound (e.g., residues of drug compounds such as antineoplastic agents or anti-inflammatory agents), and can reduce toxicity inherent to the drug compound, per se. Furthermore, the DDS compound of the present invention also has excellent blood vessel permeability. Since [[s]] protease (peptidase) is expressed at tumorous sites or inflammatory sites, the DDS compound having a spacer comprising an oligopeptide is readily hydrolyzed at the spacer moiety to allow the released drug compound to be incorporated into cells and exhibit its efficacy, or the DDS compound is taken into the cells with the aid of a receptor present in a target cell which recognizes the saccharide, and the drug compound released by the action of a protease exhibits its efficacy.

Please replace the paragraph appearing at page 27, penultimate line to page 28, line 12 with the following amended paragraph:

A DDS compound (Compound 1) in which a carboxymethyldextran polyalcohol (occasionally abbreviated as "CM-Dex-PA" or "CM-dextran polyalcohol" hereinafter in the examples) as a polymer carrier and an antineoplastic agent ((1S,9S)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13(9H,15H)-dione disclosed in claim 2 of Japanese Patent Unexamined Publication (KOKAI) (Hei) No. 6-87746/1994 (abbreviated as "DX-8951" in hereinafter in the examples) were bound by means of a tetrapeptide spacer represented as -Gly-Gly-Phe-Gly- (SEQ ID NO. 1) (the oligopeptide is shown as the sequence from their N-terminals, and others are shown in the same manner hereinafter in the examples) was produced according to the method described in Example 15 of International Publication WO97/46260. As the CM-Dex-PA, that having an average molecular weight of 228K, and a carboxymethylation degree (degree of substitution with carboxymethyl groups per constitutional saccharide residue) of 0.4 was used.

Please replace the paragraph appearing at page 29, lines 1 to 8 with the following amended paragraph:

A DDS compound (Compound 2) in which CM-Dex-PA and DX-8951 were bound by means of a spacer represented by -Gly-Gly-Gly-Phe-NH-$(CH_2)_4$-CO- (SEQ ID NO.8) was prepared as follows. 5-Aminopentanoic acid (1.0 g), p-toluenesulfonic acid (1.95 g), and benzyl alcohol (5 ml) were allowed to react in toluene (50 ml) at 140°C for 5 hours while removing the produced water by using a Dean-Stark apparatus. The reaction mixture was concentrated, and

the resulting residue was solidified by adding ether. The solid obtained was filtrated, washed with ether, and dried to obtain 2.9 g of tosylic acid salt of 5-aminopentanoic acid benzyl ester.

Please replace the paragraph appearing at page 29, line 9 to page 30, line 6 with the following amended paragraph:

Boc-Gly-Gly-Gly-Phe-OH (575 mg) (SEQ ID NO. 8), HOSu (182 mg), and DCC (326 mg) were dissolved in DMF (20 ml), and the mixture was stirred for 30 minutes. The solution was added with a solution of p-toluenesulfonic acid salt of 5-aminopentanoic acid benzyl ester (500 mg) and triethylamine (0.184 ml) dissolved in DMF (10 ml), and the mixture was stirred for 3 days at room temperature. The reaction mixture was concentrated, and the residue was purified by column chromatography (CH_2Cl_2:MeOH = 20:1) to obtain 380 mg of Boc-Gly-Gly-Gly-Phe-NH-$(CH_2)_4$-COOBzl (Bzl represents benzyl group) (SEQ ID NO. 8). The Boc-Gly-Gly-Gly-Phe-NH-$(CH_2)_4$-COOBzl (SEQ ID NO. 8) (380 mg) was dissolved in methanol containing 50% of water (20 ml), and the solution was added with 5% Pd-C (water content; 50%, 300 mg) and stirred overnight under hydrogen at ordinary pressure. The catalyst in the reaction mixture was removed by filtration, and the filtrate was concentrated to dryness to obtain Boc-Gly-Gly-Gly-Phe-NH-$(CH_2)_4$-COOH (SEQ ID NO. 8) (330 mg).

Please replace the paragraph appearing at page 30, lines 7 to 23 with the following amended paragraph:

The Boc-Gly-Gly-Gly-Phe-NH-$(CH_2)_4$-COOH (SEQ ID NO. 8) (150 mg), DCC (70 mg) and HOSu (40 mg) were dissolved in DMF, and the solution was stirred for 30 minutes. A solution of DX-8951 (160 mg) and triethylamine (0.040 ml) dissolved in DMF was added to the above solution, and then the mixture was stirred overnight at room temperature. The reaction mixture was concentrated, and the resulting residue was purified by column chromatography (CH_2Cl_2:MeOH = 20:1) to obtain Boc-Gly-Gly-Gly-Phe-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 8) (110 mg). The Boc-Gly-Gly-Gly-Phe-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 8) (110 mg) was dissolved in TFA (2 ml), and the solution was allowed to react for 1 hour. The reaction mixture was concentrated, and the resulting residue was solidified by addition of ether. The supernatant was removed, and the solid was dried to obtain 100 mg of trifluoroacetic acid salt of H-Gly-Gly-Gly-Phe-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 8).

^{1}H-NMR (DMSO-d_6): δ 8.45-8.55 (m, 2H), 8.28-8.35 (m, 2H), 7.95-8.10 (br, 2H), 7.79 (d, 1H, J=10.7Hz), 7.70-7.75 (m, 1H), 7.32 (s, 1H), 7.20-7.30 (m, 5H), 7.15-7.25 (m, 4H), 6.50-6.60 (br, 1H), 5.50-5.60 (m, 1H), 5.40-5.50 (m, 2H), 5.18 (s, 2H), 4.50-4.60 (m, 1H), 3.55-3.95 (m, 7H), 3.00-3.25 (m, 5H), 2.75-2.85 (m, 1H), 2.50 (s, 3H), 2.15-2.25 (m, 4H), 1.86-2.00 (m, 2H), 1.55-1.65 (m, 2H), 1.45-1.55 (m, 2H), 0.88 (t, 3H, J=7.35Hz)

Please replace the paragraph appearing at page 30, line 25 to page 31, line 11 with the following amended paragraph:

CM-Dex-PA (350 mg) produced by the method described in Example 13 of ~~Japanese Patent Unexamined Publication (KOKAI) (Hei) No. 8-144421/1996,~~ WO 97/46260, having an average molecular weight of 337K and a carboxymethylation degree (degree of substitution with carboxymethyl groups per constitutional saccharide residue) of 0.4, was dissolved in water (10 ml). To this solution, a solution of trifluoroacetic acid salt of H-Gly-Gly-Gly-Phe-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 8) (50 mg) dissolved in methanol (10 ml) was added, and the mixture was further added with a solution of HOBt (7 mg) dissolved in methanol (5 ml). The reaction mixture was adjusted to pH 7.0, added with water-soluble carbodiimide (10 mg), and then the mixture was stirred for 14 hours. The reaction mixture was further added with water-soluble carbodiimide (10 mg), stirred for 2 hours, and then added with water-soluble carbodiimide (10 mg) and stirred for 2 hours. The reaction mixture was diluted with ultrapure water, and the low molecular weight substances were removed by using an ultrafiltration membrane (50K). The filtrate was lyophilized, and the resulting powder was dissolved in 3 M aqueous NaCl, and the solution was added dropwise to ethanol. The deposited solid was separated by centrifugation. After the supernatant was removed, the solid was dissolved in water again. The low molecular weight substances were removed with an ultrafiltration membrane (50K), and the filtrate was passed through a 0.22 μm filter, and lyophilized to obtain 280 mg of the target compound.

Please replace the paragraph appearing at page 38, line 1 with the following amended paragraph:

(C) Synthesis of galactose-modified CM-dextran polyalcohol-Gly-Gly-Phe-Gly-DX-8951 (SEQ ID NO. 1)

Please replace the paragraph appearing at page 38, line 2 to the end of page 30 with the following amended paragraph:

The sodium salt (1.0 g) of the galactose-modified CM-dextran polyalcohol obtained in the above (B) was dissolved in water (30 ml), and the solution was added with a solution of trifluoroacetic acid salt of Gly-Gly-Phe-Gly-DX-8951 (150 mg) (SEQ ID NO. 1) and 1-hydroxybenzotriazole (35 mg) in methanol (40 ml). The solution was adjusted to pH 7.0, and then added with water-soluble carbodiimide hydrochloride (35 mg) 3 times every 2 hours and stirred overnight. The solvent in the reaction mixture was removed by evaporation, and the resulting residue was dissolved in 3 M aqueous sodium chloride (20 ml), and the solution was added dropwise to ethanol (100 ml). The deposited precipitates were collected by centrifugation (3500 rpm, 8 minutes). The precipitates were dissolved in water and desalted by ultrafiltration using a Biomax-3 membrane. The residual solution, which did not pass through the membrane, was filtered through a Millipore filter (0.22 μm), and lyophilized to obtain 900 mg of the title compound. The resulting product was dissolved in 0.1 M aqueous sodium chloride, and analyzed by GPC (column; TOSOH TSK GelPW-4000XL, solvent; 0.1 M aqueous NaCl, flow rate; 0.8 ml/min). The results of the GPC analysis and an ultraviolet absorption spectrum (in 0.1 M Tris buffer, pH 9.0) of the compound are shown in Figs. 3 and 4, respectively. The DX-8951

content in the compound was found as 4.9% (w/w) by quantitative analysis based on absorption spectrophotometry at 366 nm in 0.1 M Tris buffer containing 30% of acetonitrile (pH 10.0).

Please replace the paragraph appearing at page 39, line 1 with the following amended paragraph:

(D) Synthesis of CM-dextran polyalcohol-Gly-Gly-Phe-Gly-DX-8951 (SEQ ID NO. 1)

Please replace the paragraph appearing at page 39, line 2 to page 40, line 1 with the following amended paragraph:

The sodium salt of the CM-dextran polyalcohol obtained in the above (B) (2.0 g) was dissolved in water, and the solution was passed through Dowex-50 WX8 (Et_3NH^+) to obtain triethylammonium salt of CM-dextran polyalcohol (1.9 g). The resulting triethylammonium salt of CM-dextran polyalcohol (1.9 g) was dissolved in an aqueous solution containing 50% of N,N-dimethylformamide. The solution was successively added with a solution of triethylamine (0.112 ml) and trifluoroacetic acid salt of Gly-Gly-Phe-Gly-DX-8951 (SEQ ID NO. 1) (350 mg) in N,N-dimethylformamide (10 ml), and 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroxyquinoline (1.9 g), and the mixture was allowed to react overnight at room temperature with stirring. The solvent in the reaction mixture was removed by evaporation, and the resulting residue was dissolved in 3 M aqueous sodium chloride (20 ml), and the solution was added dropwise to ethanol (100 ml). The deposited precipitates were collected by centrifugation (3500 rpm). These precipitates were dissolved in water, and desalted by ultrafiltration using a Biomax-3 membrane. The residual solution that did not pass through the membrane was filtered by a Millipore filter (0.22 μm), and

lyophilized to obtain 1.4 g of the title compound. The resulting product was dissolved in 0.1 M aqueous sodium chloride, and analyzed by GPC (column; TOSOH TSK GelPW-4000XL, solvent; 0.1 M aqueous NaCl, flow rate; 0.8 ml/min). The result of the GPC analysis and ultraviolet absorption spectrum (in 0.1 M Tris buffer, pH 9.0) of the compound are shown in Figs. 6 and 9, respectively. The DX-8951 content in the compound was found as 5.2% (w/w) by quantitative analysis based on absorption spectrophotometry at 366 nm in 0.1 M Tris buffer containing 30% of acetonitrile (pH 10.0).

Please replace the paragraph appearing at page 39, line 2 to page 40, line 1 with the following amended paragraph:

The resulting sodium salt of galactose-modified CM-dextran polyalcohol (200 mg) was dissolved in water (3 ml), and the solution was added with a solution of trifluoroacetic acid of Gly-Gly-Phe-Gly-DX-8951 (SEQ ID NO. 1) (27 mg) in methanol (3 ml) and a solution of 1-hydroxybenzotriazole (7 mg) in methanol (3 ml). The resulting solution was adjusted to pH 7.0, added with water-soluble carbodiimide hydrochloride (7 mg) 3 times every 2 hours, and stirred overnight. The solvent in the reaction mixture was removed by evaporation, and the resulting residue was dissolved in 3 M aqueous sodium chloride (10 ml), and then the solution was added dropwise to ethanol (100 ml). The deposited precipitates were collected by centrifugation (3500 rpm). The precipitates were dissolved in water, and desalted by ultrafiltration using a Biomax-50 membrane. The residual solution that did not pass through the membrane was filtered by a Millipore filter (0.22 μm), and lyophilized to obtain 180 mg of the title compound. The product was dissolved in 0.1 M aqueous sodium chloride, and analyzed by GPC (column; TOSOH TSK

GelPW-4000XL, solvent; 0.1 M NaCl aqueous solution, flow rate; 0.8 ml/min). The result of the GPC analysis and an ultraviolet absorption spectrum (in 0.1 M Tris buffer, pH 9.0) of the product are shown in Figs. 7 and 10, respectively. The DX-8951 content in the product was and found as 3.7% (w/w) by quantitative analysis based on absorption spectrophotometry at 366 nm in 0.1 M Tris buffer containing 30% of acetonitrile (pH 10.0).

Please replace the paragraph appearing at page 44, lines 1 to 2 with the following amended paragraph:

Example 9: Synthesis of N-acetylgalactosamine-modified CM-dextran polyalcohol-Gly-Gly-Phe-Gly-DX-8951 (SEQ ID NO. 1)

Please replace the paragraph appearing at page 44, line 15 to page 45, line 12 with the following amended paragraph:

The resulting N-acetylgalactosamine-modified CM-dextran polyalcohol (200 mg) was dissolved in water (10 ml), and the solution was added with a solution of trifluoroacetic acid salt of Gly-Gly-Phe-Gly-DX-8951 (SEQ ID NO. 1) (30 mg) dissolved in methanol (10 ml), and a solution of 1-hydroxybenzotriazole (30 mg) dissolved in methanol (10 ml). The solution was adjusted to pH 7.0, and added with water-soluble carbodiimide hydrochloride (10 mg) 3 times every 2 hours. The mixture was stirred for 2 hours, and adjusted to pH 8.5. Low molecular weight fractions in the reaction mixture was removed by ultrafiltration using a Biomax -50 membrane. The residual solution that did not pass through the membrane was filtered through a Millipore filter (0.22 μm) and lyophilized to obtain the title compound (203 mg). The resulting

product was dissolved in 0.1 M aqueous sodium chloride and then analyzed by GPC (column; TOSOH TSK Gel PW-6000XL, solvent; 0.1 M acetate buffer (pH 5.0) containing 20% of acetonitrile, flow rate; 0.8 ml/min). The result of the GPC analysis and an ultraviolet absorption spectrum of this compound (0.1 M Tris buffer (pH 10.0):acetonitrile = 7:3, 0.16 mg/ml) are shown in Figs. 8 and 11, respectively. The content of drug compound residue in the product was found as 4.6% (w/w) by quantitative analysis based on absorption spectrophotometry at 366 nm in 0.1 M Tris buffer (pH 10.0):acetonitrile = 7:3.

Please replace the paragraph appearing at page 45, lines 13 to 14 with the following amended paragraph:

Example 10: Measurement of DX-8951 content in CM-Dex-PA-Gly-Gly-Phe-Gly-NH-Y'-CH_2-O-CO-DX-8951 (SEQ IS NO. 1)

Please replace the paragraph appearing at page 45, lines 15 to 29 with the following amended paragraph:

5 µl of a solution of CM-Dex-PA-Gly-Gly-Phe-Gly-NH-Y'-CH_2-O-CO-DX-8951 (SEQ ID NO. 1) (Y' means p-phenylene group) prepared as 1 mg/ml in distilled water was added with 95 µl of a papain solution prepared as 2 mg/ml in Britton Robinson buffer (pH 6). The reaction mixture was incubated at 40°C for 4 hours, added with 100 µl of 0.5 N HCl solution containing 50% of acetonitrile, and content of the released hydrolysate [DX-8951] was determined by HPLC. For the HPLC analysis, a Symmetry C18 (4.6 x 100 mm; 3.5 μm, Watars Co.) column was used, and elution was performed with a 0.1% trifluoroacetic acid solution supplemented with

an organic solvent (methanol:acetonitrile = 1:2) so as to be a gradient from 20 to 70% for 12 minutes, and the hydrolysate was detected by fluorescent spectroscopy (Ex. 375 nm and Em. 445 nm). As the result, DX-8951 was eluted at about 5.7 minutes. The DX-8951 content in the above DDS compound was calculated as 4.0% by using a calibration curve prepared with DX-8951. On the other hand, the DX-8951 content was calculated as 3.3% based on UV absorption of the aforementioned DDS compound by using a calibration curve prepared with DX-8951.

Please replace the paragraph appearing at page 45, last line to page 46, line 1 with the following amended paragraph:

Example 11: Measurement of DX-8951 content in CM-Dex-PA-Gly-Gly-Gly-Phe-NH-Y'-CH_2-O-CO-DX-8951 (SEQ ID NO. 8)

Please replace the paragraph appearing at page 46, lines 2 to 16 with the following amended paragraph:

5 μl of a solution of CM-Dex-PA-Gly-Gly-Gly-Phe-NH-Y'-CH_2-O-CO-DX-8951 (SEQ ID NO. 8) prepared as 1 mg/ml in distilled water was added with 95 μl of a solution of α-chymotrypsin prepared as 2 mg/ml in Britton Robinson buffer (pH 6). The reaction mixture was incubated at 40°C for 4 hours and then added with 100 μl of 0.5 N HCl solution containing 50% of acetonitrile, and the content of the released hydrolysate [DX-8951] was determined by HPLC. For the HPLC alnalysis, a Symmetry C18 (4.6 x 100 mm; 3.5 μm, Watars Co.) column was used, and elution was performed with a 0.1% trifluoroacetic acid solution supplemented with an organic solvent (methanol:acetonitrile = 1:2) so as to be a gradient from 20 to 70% for 12

minutes, and the hydrolysate was detected by fluorescent spectroscopy (Ex. 375 nm and Em. 445 nm). As a result, DX-8951 was eluted at about 5.7 minutes. The DX-8951 content in the above DDS compound was calculated as 2.5% by using a calibration curve prepared with DX-8951. On the other hand, the DX-8951 content was calculated as 1.7% based on UV absorption of the aforementioned DDS compound by using a calibration curve prepared with DX-8951.

Please replace the paragraph appearing at page 46, lines 17 to 18 with the following amended paragraph:

Example 12: Measurement of DX-8951 content in CM-Dex-PA-Gly-Gly-Phe-Gly-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 1)

Please replace the paragraph appearing at page 46, line 19 to page 47, line 2 with the following amended paragraph:

5 μl of a solution of CM-Dex-PA-Gly-Gly-Phe-Gly-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 1) prepared as 100 μg/ml in distilled water was added with 95 μl of a papain solution prepared as 2 mg/ml in Britton Robinson buffer (pH 6). The reaction mixture was incubated at 40°C for 4 hours and then added with 100 μl of 0.5 N HCl solution containing 50% of acetonitrile, and the content of the released hydrolysate [NH_2-$(CH_2)_4$-CO-DX-8951] was determined by HPLC. For the HPLC analysis, a Symmetry C18 (4.6 x 100 mm; 3.5 μm, Watars Co.) column was used, and elution was performed with 0.1% trifluoroacetic acid solution containing 32% of organic solvent (methanol:acetonitrile = 1:2), and the hydrolysate was detected by fluorescent spectroscopy (Ex. 375 nm and Em. 445 nm). As a result, the NH_2-

$(CH_2)_4$-CO-DX-8951 was eluted at about 5.3 minutes. The DX-8951 content in the above DDS compound was calculated as 3.0% by using a calibration curve prepared with NH_2-$(CH_2)_4$-CO-DX-8951. On the other hand, the DX-8951 content was calculated as 3.1% based on UV absorption of the aforementioned DDS compound by using a calibration curve prepared with DX-8951.

Please replace the paragraph appearing at page 47, lines 3 to 4 with the following amended paragraph:

Example 13: Measurement of DXR content in CM-Dex-PA-Gly-Gly-Phe-Gly-DXR (DXR: doxorubicin) (SEQ ID NO. 1)

Marked up copy of amended paragraph appearing at page 47, line 18:

Example 14: Synthesis of CM-dextran polyalcohol-Gly-Gly-Phe-Gly-DXR (SEQ ID NO. 1)

Please replace the paragraph appearing at page 47, line 19 to page 48 line 3 with the following amended paragraph :

Sodium salt of carboxymethyldextran polyalcohol (30 mg) having an average molecular weight of 274K and a carboxymethylation degree (degree of substitution with carboxymethyl groups per constitutional saccharide residue) of 0.4, which was prepared according to the method described in Example 24 of WO97/46260, was dissolved in 0.05 M collidine-HCl buffer (2 ml) containing 50% of methanol. The solution was added with a solution of hydrochloride of Gly-Gly-Phe-Gly-DXR (SEQ ID NO. 1) (4 mg) in methanol (400 μl), which hydrochloride was

prepared according to the method described in Example 43 of WO97/46260, and a solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.4 mg) in methanol (240 μl), and stirred for 2 hours. The solution was added with 30 ml of 3 M brine, and desalted by ultrafiltration using a Biomax-50K membrane. The residual solution that did not pass through the membrane was filtered by a Millipore filter (0.22 μm), and lyophilized to obtain the title compound (25 mg). The content of the drug compound residue in this compound was determined as 4.3% (w/w) by absorption spectrophotometry at 480 nm in PBS (pH 7.4).

Please replace the paragraph appearing at page 48, line 4 with the following amended paragraph:

Example 15: Synthesis of CM-Dex-PA-Gly-Gly-Phe-Gly-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 1)

Please replace the paragraph appearing at page 48, lines 5 to 17 with the following amended paragraph:

Boc-Gly-Gly-Phe-Gly-OH (SEQ ID NO. 1) (575 mg), HOSu (182 mg), and DCC (326 mg) were dissolved in DMF (20 ml), and the solution was stirred for 30 minutes. The resulting solution was added with a solution of p-toluenesulfonic acid salt of 5-aminopentanoic acid benzyl ester (500 mg) and triethylamine (0.184 ml) dissolved in DMF (10 ml), and the mixture was stirred at room temperature for three days. The reaction mixture was concentrated, and the residue was purified by column chromatography (CH_2Cl_2:MeOH = 20:1) to obtain 560 mg of Boc-Gly-Gly-Phe-Gly-NH-$(CH_2)_4$-COOBzl (SEQ ID NO. 1). The Boc-Gly-Gly-Phe-Gly-NH-

$(CH_2)_4$-COOBzl (SEQ ID NO. 1) (560 mg) was dissolved in methanol (60 ml) containing 50% of water, and the solution was added with 5% Pd-C (water content; 50%, 1.5 g) and stirred overnight under hydrogen at ordinary pressure. After the catalyst was removed from the reaction mixture by filtration, the mixture was concentrated to dryness to obtain 300 mg of Boc-Gly-Gly-Phe-Gly-NH-$(CH_2)_4$-COOH (SEQ ID NO. 1).

Please replace the paragraph appearing at page 48, lines 18 to 24 with the following amended paragraph:

The Boc-Gly-Gly-Phe-Gly-NH-$(CH_2)_4$-COOH (SEQ ID NO. 1) (300 mg), DCC (138 mg) and HOSu (77 mg) were dissolved in DMF, and the solution was stirred for 30 minutes. The resulting solution was added with a solution of DX-8951 (317 mg) and triethylamine (0.078 ml) dissolved in DMF, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated, and the resulting residue was purified by column chromatography (CH_2Cl_2:MeOH = 10:1) to obtain 400 mg of Boc-Gly-Gly-Phe-Gly-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 1).

Please replace the paragraph appearing at page 48, line 25 to page 49, line 3 with the following amended paragraph:

The Boc-Gly-Gly-Phe-Gly-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 1) (300 mg) was dissolved in TFA (2 ml), and the solution was allowed to react for one hour, and then the reaction mixture was concentrated. The resulting residue was solidified by addition of ether, and the

supernatant was removed. The solid mass was dried to obtain 250 mg of trifluoroacetic acid salt of H-Gly-Gly-Phe-Gly-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 1).

^{1}H-NMR(DMSO-d_6): δ 8.45-8.55 (m, 2H), 8.28-8.35 (m, 2H), 7.95-8.10 (br, 2H), 7.79 (d, 1H, J=10.7Hz), 7.70-7.75 (m, 1H), 7.32 (s, 1H), 7.20-7.30 (m, 5H), 7.15-7.25 (m, 4H), 6.50-6.60 (br, 1H), 5.50-5.60 (m, 1H), 5.40-5.50 (m, 2H), 5.18 (s, 2H), 4.50-4.60 (m, 1H), 3.55-3.95 (m, 7H), 3.00-3.25 (m, 5H), 2.75-2.85 (m, 1H), 2.50 (s, 3H), 2.15-2.25 (m, 4H), 1.86-2.00 (m, 2H), 1.55-1.65 (m, 2H), 1.45-1.55 (m,2H), 0.88 (t, 3H, J=7.35Hz)

Please replace the paragraph appearing at page 49, lines 4 to 15 with the following amended paragraph:

Triethylammonium salt of carboxymethyldextran polyalcohol (200 mg) having an average molecular weight of 337K and a carboxymethylation degree (degree of substitution with carboxymethyl groups per constitutional saccharide residue) of 0.4, which was prepared according to the method described in Example 24 of WO97/46260, was dissolved in DMF (10 ml). The above solution was added with a solution of trifluoroacetic acid salt of H-Gly-Gly-Phe-Gly-NH-$(CH_2)_4$-CO-DX-8951 (SEQ ID NO. 1) (30 mg) and triethylamine (10 μl) in methanol (4 ml), further added with a solution of 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroxyquinoline (200 mg) in methanol (3 ml), and stirred overnight at room temperature with light shielding. The reaction mixture was diluted with 3 M brine, and low molecular weight fractions were removed by an ultrafiltration membrane (50K), and the resulting residue was passed through a 0.22 μm filter and lyophilized to obtain 178 mg of the target compound.